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Scrub typhus: pathophysiology, clinical manifestations and prognosis

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ABSTRACT

Scrub typhus is a zoonosis caused by the pathogen *Orientia tsutsugamushi* (*O. tsutsugamushi*). The disease has significant prevalence in eastern and Southeast Asia. Usually presenting as an acute febrile illness, the diagnosis is often missed because of similarities with other tropical febrile infections. Many unusual manifestations are present, and these are described in this review, together with an outline of current knowledge of pathophysiology. Awareness of these unusual clinical manifestations will help the clinician to arrive at an early diagnosis, resulting in early administration of appropriate antibiotics. Prognostic indicators for severe disease have not yet been clearly established.

1. Introduction

Scrub typhus is a vector borne zoonosis caused by the organism *Oricntia tsutsugamushi* (*O. tsutsugamushi*). This acute febrile illness is endemic in many countries in eastern and south-east Asia and northern Australia[1]. Trombiculid mites (*Leptotrombidium deliense*, *L. palladium etc*) are the natural hosts of the pathogen. The infected larval stages of mites (chiggers) inoculate humans (accidental hosts) while feeding. The pathogens multiply at the site of entry which later develops in to an eschar[2] and this is followed by a febrile illness, with many clinical manifestations. It is estimated that 1 million new cases appear annually and 1 billion people are at risk of infection[3].

The incidence of cases of scrub typhus has been increasing since the early eighties[4]. While some attribute this to the appearance of new strains of pathogens, it is also possible that cases were misdiagnosed or under-diagnosed in the past, thus underestimating the mortality and morbidity due to the disease. It is difficult to conclude whether this is an already existent yet unappreciated prevalence or a true rise in incidence[5-7]. For example, assessment of patients with prolonged undiagnosed fever in Southern India and Sri Lanka by serological examination have shown that a significant proportion (9.2%-37.5%) had evidence of current and past infection with scrub typhus[8,9].

While in many instances a simple febrile illness, scrub typhus has potentially fatal outcome with multiple organ dysfunction in severe cases[10]. Estimates of mortality rates from scrub typhus lie between 0%-30% in untreated patients[11]. Clinical manifestations can be diverse, and this brief review summarizes the pathophysiology of the disease, the different clinical manifestations, and their relationship to prognosis.

2. Methods

We searched PUBMED using the keywords 'scrub typhus' or '*O. tsutsugamushi*' in any field. The search was restricted to articles published in English within the last 15 years (1994-2009) as they would contain more recent data. We screened all abstracts for relevance, *i.e.*, data on clinical manifestations and presentations, pathophysiology, and prognosis (independent coding by three reviewers). Suitable data was available in 112 sources. Data sources included; reviews published in core clinical journals, cohort studies, interventional studies, clinical trials and cross sectional analyses. Hundred and one papers were reviewed from a selected 112 (90.2%).

3. Pathophysiology

O. tsutsugamushi survives in the wild in a cycle involving trombiculid mites (principal vectors) and other vertebrates

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(small mammals and birds). Humans are accidental hosts for the pathogen. *O. tsutsugamushi* is different from rickettsia in its genetic makeup, cell wall structure and many authors now agree that it is an obligate intracellular gram negative bacterium[12]. The larval stage of the mites (chiggers) harbouring the bacterium, bite exposed individuals in vulnerable niches such as forests and mite infested undergrowth during occupational and recreational activities. Following the bite, the pathogen multiplies at the site of inoculation and subsequently induces local and systemic manifestations of infection[13].

The severity of illness depends on both host and pathogen related factors. Pathogen related factors may be attributed to the fact that different strains (Karp, Gilliam *etc.*) of *O. tsutsugamushi* may contribute differently to disease severity. Human hosts with G6PD deficiency are shown to have a worse prognosis than healthy individuals[14,15]. It is now established that the bacterium multiplies and disseminates within the human host and its principal target site is the endothelial cells. They have been located in endothelial cells of heart, lung, brain, liver, kidney, pancreas, skin and also isolated from macrophages of liver and spleen in post mortem samples[16]. Initially it was thought that the organism gains entry to the target organs through the lymphatic system. However in 2001, Walsh *et al*[17] have demonstrated the pathogen within mononuclear white blood cells in patients with acute infection, suggesting the possibility of a direct blood borne spread.

The immune response induced by *O. tsutsugamushi* is a combination of humoral and cell mediated immunity. The rise of cytokines during an acute infection was demonstrated as far back as 1997 by Iwasaki *et al*[18]. In a small series of patients, they have shown a significant rise in macrophage colony stimulating factor (M-CSF), interferon gamma (IFN-γ) and granulocyte colony stimulating factor (G-CSF). Only a few patients showed a rise in tumour necrosis factor (TNF-α) during the infection but it continued to rise during convalescence in those who had severe disease. These observations demonstrated that the macrophage and T lymphocyte response may be the driving factor in immunity against infection. More recently, de Fost *et al*[19] have demonstrated indirect evidence for cytotoxic lymphocyte (cytotoxic T cell and natural killer cell) activation during acute infection that may play a key role in destroying the infected host cells.

The parasite has evolved to evade the immune mechanisms of the host. Given the high mortality rate of untreated disease, these mechanisms are of clinicopathological significance. Cho *et al*[20] showed that live *O. tsutsugamushi* down regulates the expression of the glycoprotein 96 (gp96) in infected macrophages and endothelial cells compared to non- infected cells in cell culture. This molecule is expressed in the endoplasmic reticulum of cells and plays a central role in major histocompatibility complex class I (MHC I) mediated antigen presentation, functioning of dendritic cells, antibody production and cross priming of immune cells[20]. Suppression of this glycoprotein may be one mechanism by which the pathogen neutralizes the host immune response.

The relationship between *O. tsutsugamushi* infection and HIV is of interest in current context. Watt *et al*[21] for the first time demonstrated that HIV viral load fell during acute infection with scrub typhus in HIV positive individuals and serum samples from patients with acute typhus suppressed HIV-1 *in vitro*. A plausible hypothesis was that a humoral factor induced by acute infection suppressed HIV activity. However the authors failed to identify this molecule though there were several suggestions[22]. Several queries were raised regarding the methodology (small sample size, viral load measurements *etc.*)[23,24] of this initial observation. Another follow up study however, has shown further supportive evidence. Infusion of plasma from patients with mild acute scrub typhus, reduced viral loads in 7 out of 10 patients with HIV-1 infection. The beneficial effect was observed up to 8 weeks after a single transfusion. However, the in vivo impact of donor plasma was not seen in all HIV infected patients[25]. Several hypotheses have been developed to explain these observations including an inhibitory antibody mediated response, restriction of syncytia forming/maintenance of non syncytia inducing phenotypes of virus and specific activity against certain strains of the HIV virus[26]. However the actual mechanism for this observation remains an enigma.

4. Clinical manifestations

The incubation period of *O. tsutsugamushi* in humans is around 10-12 d (can vary between 6-21 d)[13]. The clinical manifestations vary in severity from a mild febrile illness to a severe potentially fatal disease with multi organ dysfunction syndrome (MODS). The typical systemic features of infection are well known and include fever, gastrointestinal disturbances, malaise, cough, myalgia and headache[13]. A maculopapular rash starting on the trunk and spreading in to the limbs is seen towards the end of the first week (since the onset of fever)[13]. Regional lymphadenopathy is commonly observed.

Another significant finding is an eschar at the bite site which is almost diagnostic. The prevalence of eschars in patients diagnosed with scrub typhus have been reported as between 7%-80%[27-29]. Difficulty in detecting small eschars in dark skinned individuals, eschar inducing capacity of different strains of *O. tsutsugamushi* and atypical appearance of eschars in areas of damp and moist skin may be the reason for this difference. The eschar starts as a small papule that enlarges and subsequently undergoes central necrosis to turn black. The common sites for finding an eschar are groin, axilla, waist and other exposed parts of the body. Kim *et al*[27] for the first time showed different patterns of eschar distribution in males and females. Authors attributed this to differences in skin folds, clothing and pressure points created by undergarments. The front of the chest and the area within 30 cm from the umbilicus were common sites for both sexes while lower limbs and back were also common areas for males and females respectively. However, the findings in other communities, where there are different gendered patterns in clothing and outdoor activities may reveal different results.

From the second week onwards, a proportion of patients (especially those with untreated disease) will show evidence of systemic infection. This stage of illness can attack different organ systems such as the central nervous system (acute diffuse encephalomyelitis, encephalopathy, meningitis, deafness, cranial nerve palsies, eye manifestations)[30-35], cardiovascular system (rhythm abnormalities, myocardial involvement with congestive heart failure, vasculitis)[13,36,37], renal system (acute renal failure)[38-40], respiratory system (Interstitial pneumonia and acute respiratory distress syndrome)[41-44] and gastrointestinal system (alterations in liver functions, pancreatitis, diarrhoea)[45-48]. Sometimes MODS ensues[10,40,49]. Due to the wide variation in the clinical manifestations, the diagnosis of scrub typhus is often missed or made late.

5. Scrub typhus in pregnancy

The impact of scrub typhus in pregnancy is less explored. In a case series of eight patients treated for acute scrub typhus during pregnancy (confirmed by indirect immunofluorescence assay), Kim *et al*[50] describe a healthy outcome for both mothers and babies (without any congenital infections or malformations). All patients had an uncomplicated illness and gestational age at presentation varied between 10–29 weeks. However poor foetal outcome has been reported; Mathai *et al*[51] report of four women with scrub typhus in the second trimester, treated with ciprofloxacin, who all had miscarriages or still births. In another case report, an infected woman was treated with chloramphenicol successfully at 29 weeks of gestation. However the baby was born prematurely and died subsequently (no vertical transmission demonstrated) [52]. Neonatal scrub typhus has been reported in two instances with cord blood being positive for IgM[53,54]. Acute scrub typhus can be transmitted vertically but congenital malformation due to infection per se, has not been demonstrated.

6. Prognostic indicators

Given the significant sequelae of infection, early identification of indicators for a worse prognosis will help in the management. However the literature on such indicators is limited and in studies where such factors are identified, the sample sizes are too small to come to solid conclusions. Lai *et al*[55] comparing 18 patients with delayed defervescence against 88 patients with fast recovery, cite absence of headache, relative bradycardia and jaundice as predictors of delayed defervescence. However, this study analyzed patients with scrub typhus, murine typhus and Q fever together and only 7 patients with scrub typhus had delayed defervescence. It is not clear whether these predictors differed for individual infections. In addition, delayed fever can be attributed to many other factors such as resistant strains and the choice of antibiotics (all these patients were treated with doxycycline). These findings have not been confirmed by other investigators.

Sonthayanon *et al*[56] have demonstrated that higher DNA loads at admission are positively correlated with mortality and a longer duration of illness ($P<0.001$). While this is an interesting concept directly correlating bacterial burden with clinical outcome, its applicability in resource limited settings is doubtful because of the cost factor. In a retrospective epidemiological study, Lee *et al*[57] describes absence of an eschar, higher APACHE II scores and an event of ICU admission as independent risk factors associated with fatality (n=297, deaths=18). This shows a conflict in evidence with the previous study by Sonthayanon et al, who showed that the presence of an eschar was positively and significantly correlated with higher DNA loads at admission which in turn was associated with a fatal outcome. Due to such conflicts in evidence, gaps in data and small sizes of samples, it is difficult to establish clear prognostic indicators. This is an area for further research.

7. Conclusion

Scrub typhus is an important infectious disease with a potentially fatal outcome. Apart from the classical presentation as an acute febrile illness, many other unusual clinical manifestations are reported. In countries where other febrile illnesses are also commonly seen, awareness of these unusual manifestations may alert the clinician to a diagnosis of scrub typhus, enabling early administration of appropriate antibiotics. Experience with the disease in pregnancy is limited to a few case reports but vertical transmission has been demonstrated. Prognostic indicators for severe disease cannot be established with the available evidence due to limited sample sizes and conflicting results.

Conflict of interest statement

We declare that we have no conflict of interest.

References

[1] Koh GC, Maude RJ, Paris DH, Newton PN, Blacksell SD. Diagnosis of scrub typhus. *Am J Trop Med Hyg* 2010; **82**: 368–370.

[2] Pham XD, Otsuka Y, Suzuki H, Takaoka H. Detection of *Orientia tsutsugamushi* (Rickettsiales: Rickettsiaceae) in unengorged chiggers (Acari: Trombiculidae) from Oita Prefecture, Japan, by nested polymerase chain reaction. *J Med Entomol* 2001; **38**: 308–311.

[3] Watt G, Parola P. Scrub typhus and tropical rickettsioses. *Curr Opin Infect Dis* 2003; **16**: 429–436.

[4] Bang HA, Lee MJ, Lee WC. Comparative research on epidemiological aspects of tsutsugamushi disease (scrub typhus) between Korea and Japan. *Jpn J Infect Dis* 2008; **61**: 148–150.

[5] Demma LJ, McQuiston JH, Nicholson WL, Murphy SM, Marumoto P, Sengebau-Kingzio M, et al. Scrub typhus, Republic of Palau. *Emerg Infect Dis* 2006; **12**: 290–295.

[6] Durand AM, Kuartei S, Togamae I, Sengebau M, Demma L, Nicholson W, et al. Scrub typhus in the Republic of Palau, Micronesia. *Emerg Infect Dis* 2004; **10**: 1838–1840.

[7] Kweon SS, Choi JS, Lim HS, Kim JR, Kim KY, Ryu SY, et al. Rapid increase of scrub typhus, South Korea, 2001–2006. *Emerg Infect Dis* 2009; **15**: 1127–1129.

[8] Kularatne SA, Edirisingha JS, Gawarammana IB, Urakami H, Chenchittikul M, Kaiho I. Emerging rickettsial infections in Sri Lanka: the pattern in the hilly Central Province. *Trop Med Int Health* 2003; **8**: 803–811.

[9] Kamarasu K, Malathi M, Rajagopal V, Subramani K, Jagadeeshramasamy D, Mathai E. Serological evidence for wide distribution of spotted fevers & typhus fever in Tamil Nadu. *Indian J Med Res* 2007; **126**: 128–130.

[10] Cracco C, Delafosse C, Baril L, Lefort Y, Morelot C, Derenne JP, et al. Multiple organ failure complicating probable scrub typhus. *Clin Infect Dis* 2000; **31**: 191–192.

[11] David J Cennimo. Pediatric Scrub typhus. [Online]. Available from http://emedicine.medscape.com/article/971797-overview. [Accessed on January 5, 2010].

[12] Tamura A, Ohashi N, Urakami H, Miyamura S. Classification of *Rickettsia tsutsugamushi* in a new genus, Orientia gen. nov., as *Orientia tsutsugamushi* comb. nov. *Int J Syst Bacteriol* 1995; **45**: 589–591.

[13] Jeong YJ, Kim S, Wook YD, Lee JW, Kim KI, Lee SH. Scrub typhus: clinical, pathologic, and imaging findings. *Radiographics* 2007; **27**: 161–172.

[14] Hanson B. Comparative susceptibility to mouse interferons of *Rickettsia tsutsugamushi* strains with different virulence in mice and of *Rickettsia rickettsii*. *Infect Immun* 1991; **59**: 4134–4141.

[15] Walker DH, Radisch DL, Kirkman HN. Haemolysis with

rickettsiosis and glucose-6-phosphate dehydrogenase deficiency. *Lancet* 1983; **2**: 217.
[16]Moron CG, Popov VL, Feng HM, Wear D, Walker DH. Identification of the target cells of *Orientia tsutsugamushi* in human cases of scrub typhus. *Mod Pathol* 2001; **14**: 752-759.
[17]Walsh DS, Myint KS, Kantipong P, Jongsakul K, Watt G. *Orientia tsutsugamushi* in peripheral white blood cells of patients with acute scrub typhus. *Am J Trop Med Hyg* 2001; **65**: 899-901.
[18]Iwasaki H, Takada N, Nakamura T, Ueda T. Increased levels of macrophage colony-stimulating factor, gamma interferon, and tumor necrosis factor alpha in sera of patients with *Orientia tsutsugamushi* infection. *J Clin Microbiol* 1997; **35**: 3320-3322.
[19]de Fost M, Chierakul W, Pimda K, Dondorp AM, White NJ, Van der Poll T. Activation of cytotoxic lymphocytes in patients with scrub typhus. *Am J Trop Med Hyg* 2005; **72**: 465-467.
[20]Cho NH, Choi CY, Seong SY. Down-regulation of gp96 by *Orientia tsutsugamushi*. *Microbiol Immunol* 2004; **48**: 297-305.
[21]Watt G, Kantipong P, de Souza M, Chanbancherd P, Jongsakul K, Ruangweerayud R, et al. HIV-1 suppression during acute scrub-typhus infection. *Lancet* 2000; **356**: 475-479.
[22]Ikeda M, Yoshida S. HIV-1 and scrub-typhus. *Lancet* 2000; **356**: 1851.
[23]Ariyoshi K, Whittle H. HIV-1 viral load and scrub typhus. *Lancet* 2000; **356**: 1766.
[24]Colebunders R, Fransen K, Florence E, Vanham G. HIV-1 viral load and scrub typhus. *Lancet* 2000; **356**: 1765-1766.
[25]Watt G, Kantipong P, Jongsakul K, de Souza M, Burnouf T. Passive transfer of scrub typhus plasma to patients with AIDS: a descriptive clinical study. *QJM* 2001; **94**: 599-607.
[26]Kannangara S, DeSimone JA, Pomerantz RJ. Attenuation of HIV-1 infection by other microbial agents. *J Infect Dis* 2005; **192**: 1003-1009.
[27]Kim DM, Won KJ, Park CY, Yu KD, Kim HS, Yang TY, et al. Distribution of eschars on the body of scrub typhus patients: a prospective study. *Am J Trop Med Hyg* 2007; **76**: 806-809.
[28]Silpapojakul K, Chupuppakarn S, Yuthasompob S, Varachit B, Chaipak D, Borkerd T. Scrub and murine typhus in children with obscure fever in the tropics. *Pediatr Infect Dis J* 1991; **10**: 200-203.
[29]Sirisanthana V, Puthanakit T, Sirisanthana T. Epidemiologic, clinical and laboratory features of scrub typhus in thirty Thai children. *Pediatr Infect Dis J* 2003; **22**: 341-345.
[30]Chen PH, Hung KH, Cheng SJ, Hsu KN. Scrub typhus-associated acute disseminated encephalomyelitis. *Acta Neurol Taiwan* 2006; **15**: 251-254.
[31]Kim DE, Lee SH, Park KI, Chang KH, Roh JK. Scrub typhus encephalomyelitis with prominent focal neurologic signs. *Arch Neurol* 2000; **57**: 1770-1772.
[32]Kim JH, Lee SA, Ahn TB, Yoon SS, Park KC, Chang DI, et al. Polyneuropathy and cerebral infarction complicating scrub typhus. *J Clin Neurol* 2008; **4**: 36-39.
[33]Premaratna R, Chandrasena TG, Dassayake AS, Loftis AD, Dasch GA, de Silva HJ. Acute hearing loss due to scrub typhus: a forgotten complication of a reemerging disease. *Clin Infect Dis* 2006; **42**: e6-8.
[34]Nagaki Y, Hayasaka S, Kadoi C, Matsumoto M, Sakagami T. Branch retinal vein occlusion in the right eye and retinal hemorrhage in the left in a patient with classical Tsutsugamushi disease. *Jpn J Ophthalmol* 2001; **45**: 108-110.
[35]Kato T, Watanabe K, Katori M, Terada Y, Hayasaka S. Conjunctival injection, episcleral vessel dilation, and subconjunctival hemorrhage in patients with new tsutsugamushi disease. *Jpn J Ophthalmol* 1997; **41**: 196-199.
[36]Charoensak A, Chawalparit O, Suttinont C, Niwattayakul K, Losuwanaluk K, Silpasakorn S, et al. Scrub typhus: chest radiographic and clinical findings in 130 Thai patients. *J Med Assoc Thai* 2006; **89**: 600-607.
[37]Aronoff DM, Watt G. Prevalence of relative bradycardia in *Orientia tsutsugamushi* infection. *Am J Trop Med Hyg* 2003; **68**: 477-479.
[38]Kim DM, Kang DW, Kim JO, Chung JH, Kim HL, Park CY, et al. Acute renal failure due to acute tubular necrosis caused by direct invasion of *Orientia tsutsugamushi*. *J Clin Microbiol* 2008; **46**: 1548-1550.
[39]Young PC, Hae CC, Lee KH, Hoon CJ. Tsutsugamushi infection-associated acute rhabdomyolysis and acute renal failure. *Korean J Intern Med* 2003; **18**: 248-250.
[40]Hsu GJ, Young T, Peng MY, Chang FY, Chou MY, Sheu LF. Acute renal failure associated with scrub typhus: report of a case. *J Formos Med Assoc* 1993; **92**: 475-477.
[41]Wang CC, Liu SF, Liu JW, Chung YH, Su MC, Lin MC. Acute respiratory distress syndrome in scrub typhus. *Am J Trop Med Hyg* 2007; **76**: 1148-1152.
[42]Tsay RW, Chang FY. Acute respiratory distress syndrome in scrub typhus. *QJM* 2002; **95**: 126-128.
[43]Song SW, Kim KT, Ku YM, Park SH, Kim YS, Lee DG, et al. Clinical role of interstitial pneumonia in patients with scrub typhus: a possible marker of disease severity. *J Korean Med Sci* 2004; **19**: 668-673.
[44]Ichimura K, Uchida Y, Arai K, Nakazawa K, Sasaki J, Kobayashi K, et al. Afebrile scrub typhus (Tsutsugamushi disease) with acute respiratory distress syndrome. *Intern Med* 2002; **41**: 667-670.
[45]Hu ML, Liu JW, Wu KL, Lu SN, Chiou SS, Kuo CH, et al. Short report: Abnormal liver function in scrub typhus. *Am J Trop Med Hyg* 2005; **73**: 667-668.
[46]Kanno A, Yamada M, Murakami K, Torinuki W. Liver involvement in Tsutsugamushi disease. *Tohoku J Exp Med* 1996; **179**: 213-217.
[47]Wang NC, Ni YH, Peng MY, Chang FY. Acute acalculous cholecystitis and pancreatitis in a patient with concomitant leptospirosis and scrub typhus. *J Microbiol Immunol Infect* 2003; **36**: 285-287.
[48]Premaratna R, Nawasiwatte BM, Niriella MA, Chandrasena TG, Bandara NK, Rajapakse RP, et al. Scrub typhus mimicking enteric fever; a report of three patients. *Trans R Soc Trop Med Hyg* 2010; **104**: 309-310.
[49]Thap LC, Supanaranond W, Treeprasertsuk S, Kitvatanachai S, Chinprasatsak S, Phonrat B. Septic shock secondary to scrub typhus: characteristics and complications. *Southeast Asian J Trop Med Public Health* 2002; **33**: 780-786.
[50]Kim YS, Lee HJ, Chang M, Son SK, Rhee YE, Shim SK. Scrub typhus during pregnancy and its treatment: a case series and review of the literature. *Am J Trop Med Hyg* 2006; **75**: 955-959.
[51]Mathai E, Rolain JM, Verghese L, Mathai M, Jasper P, Verghese G, et al. Case reports: scrub typhus during pregnancy in India. *Trans R Soc Trop Med Hyg* 2003; **97**: 570-572.
[52]Phupong V, Srettakraikul K. Scrub typhus during pregnancy: a case report and review of the literature. *Southeast Asian J Trop Med Public Health* 2004; **35**: 358-360.
[53]Suntharasaj T, Janjindamai W, Krisanapan S. Pregnancy with scrub typhus and vertical transmission: a case report. *J Obstet Gynaecol Res* 1997; **23**: 75-78.
[54]Wang CL, Yang KD, Cheng SN, Chu ML. Neonatal scrub typhus: a case report. *Pediatrics* 1992; **89**: 965-968.
[55]Lai CH, Huang CK, Weng HC, Chung HC, Liang SH, Lin JN, et al. Clinical characteristics of acute Q fever, scrub typhus, and murine typhus with delayed defervescence despite doxycycline treatment. *Am J Trop Med Hyg* 2008; **79**: 441-446.
[56]Sonthayanon P, Chierakul W, Wuthiekanun V, Phimda K, Pukrittayakamee S, Day NP, Peacock SJ. Association of high *Orientia tsutsugamushi* DNA loads with disease of greater severity in adults with scrub typhus. *J Clin Microbiol* 2009; **47**: 430-434.
[57]Lee CS, Hwang JH, Lee HB, Kwon KS. Risk factors leading to fatal outcome in scrub typhus patients. *Am J Trop Med Hyg* 2009; **81**: 484-488.